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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,064	08/08/2006	Wolfgang Demmer	06-410	6938

20306 7590 04/24/2009

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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
04/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,064	DEMMER ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,9-15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,9-15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Picture of bacteriophage M13*.

DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/11/2009 has been entered.

Applicants' amendment cancelling Claims 2-5, 7-8 and 16; amending Claims 1, 9, 13 and 15 and adding new Claims 17-19 in the paper of 10/06/2008 is acknowledged. Claims 1, 6, 9-15 and 17-19 are pending in the instant office action and will be examined herein.

Claim Objections

2. Claim 1 is objected because of the typographical error. The "imidodiacetic acid" should be ---iminodiacetic acid".

Appropriate correction is required.

3. Claim 15 is objected to under 37 CFR 1.75 (c) as being in improper form because a **multiple dependent claim** (Any dependent claim which refers to more than one other claim ("multiple dependent claim") shall refer to such other claims in the

alternative only. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. See MPEP § 608.01 (n).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites "range of 0.01 to 12 μm, preferably in the range of 0.45 to 7 μm, and especially preferably in the range of 3 to 5 μm." A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74

(Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 12 recites the broad recitation 0.01 to 12 µm, and the claim also recites 0.45 to 7 µm and 3 to 5 µm which are the narrower statements of the range/limitation.

Withdrawn-Claim Rejections - 35 USC § 112

5. The previous rejection of Claim 13 under 35 U.S.C. 112, first paragraph, **new matter**, is withdrawn by virtue of Applicants' amendment and arguments (i.e., DEAE, CM, S and SP are known functional group for chromatographic resin evidenced by the attached Amersham Biosciences, Ion Exchange Chromatography & Chromatofocusing; and it is clear that the term "S" does not read on a genus of sulfur containing functional group, for example).

6. The previous rejection of Claims 1, 4-7 and 9-15 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of applicants' amendment.

7. The previous rejection of Claims 1, 4-7 and 9-15 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn by virtue of applicants' amendment.

Withdrawn-Claim Rejections - 35 USC § 103

8. The previous rejection of Claims 1, 4-7 and 9-15 under 35 U.S.C. 103(a) as being **unpatentable over** Sartobind® Membrane Adsorbers brochure-A (2003, see the attachment, as previously cited) **in view of** Fischer-Fruhholz (May 16, 2003, Applications Membrane Adsorbers, see the attachment, as cited previously), Sartobind® Membrane Adsorbers brochure by Hirai et al. (29, Sept 2003, Virus Purification and Removal with Sartobind® Membrane Adsorbers, see the attachment, as cited previously) and Rudgers et al. (Protein Engineering, 2001, volume 14, pages 487-492) as **evidenced** by Hondel et al. (Eur. J. biochem., Volume 68, pages 55-70) is withdrawn by virtue of using different evidentiary reference for the 35 U.S.C. 103(a) rejection as shown below in view of instant amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 6, 9-15 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sartobind® Membrane Adsorbers brochure-A (2003, see the attachment, as previously cited) in view of Fischer-Fruhholz (May 16, 2003, Applications Membrane Adsorbers, see the attachment, as cited previously), Sartobind® Membrane Adsorbers brochure by Hirai et al. (29, Sept 2003, Virus Purification and Removal with Sartobind® Membrane Adsorbers, see the attachment, as cited previously) and

Rudgers et al. (Protein Engineering, 2001, volume 14, pages 487-492) as evidenced by **Harvey et al.** (PNAS, June 22, 2004 Vol. 101, pages 9193-9198).

Sartobind® Membrane Adsorbers brochure-A teach a method of purification using "Sartobind MultiSep Membrane Adsorbers" which is used in chromatography as shown in the figures on page 5, wherein the membrane type includes "**Sartobind IDA (iminodiacetic acid) metal chelate**", wherein the applications includes "Viral purification" (see middle, under the Application on page 6). Thus, Sartobind® Membrane Adsorbers brochure teach a step of applying a solution containing high molecular biopolymers as exemplified by the graph showing the UV detection vs. flow rate of a column chromatography (see page 2) and separating virus as indicated under "Applications" (see page 6, middle); and meets the limitation of claim 1, 3 and 8 except that the virus is filamentous virus with a molecular weight of $1x10^6$. The Sartobind® Membrane Adsorbers is made of "cellulose" (see top of page 1) and have pore size of "**3-5 um**" (see top of page 4), which meets the limitation of newly added claims 17-19.

Sartobind® Membrane Adsorbers being able to use Cu^{2+} is evidenced by the teaching of charging with Cu^{2+} by Fischer-Fruhholz (see page 5); thus, meeting the limitation of claims 4-5.

Sartobind® Membrane Adsorbers brochure by Hirai et al. teach that the Sartobind® Membrane Adsorbers is used to purify a virus including "pseudorabies virus (PrV)" on page 32 as an example.

Sartobind® Membrane Adsorbers brochure-A **does not** teach a method for purifying a filamentous virus M13 and with additional method step of additional ion

exchange chromatography prior to step (a) of Claim 1, or additional filtration for the removal of additional impurities as recited in Claim 9.

Harvey et al. teach a filamentous bacteriophage M13 which is "the oldest and currently most widely used protein library-screening method" (see bottom of left column page 9193).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a solution containing M13 bacteriophage virus to the membrane type includes Sartobind IDA (iminodiacetic acid) Cu^{2+} metal chelate for viral purification with reasonable expectation of success, because the metal chelate affinity membrane of Sartobind have "affinity to His, Cys, Trp present in almost every protein" (see page 5 of Fischer-Fruhholz) wherein the M13 phage has been used to display expresses a protein of interest on the surface of the M13 bacteriophage. One skilled in the art would have been motivated to separate the M13 bacteriophage using Sartobind IDA (iminodiacetic acid) Cu^{2+} metal chelate provided by Sartorius company since it teaches the "application of Sartobind Membrane Adsorbers is advantageous especially in purification and removal of viruses for biopharmaceutical process" (see Sartobind® Membrane Adsorbers brochure by Hirai et al., Summary at the end) wherein the bacteriophage M13 is the oldest and currently most widely used protein library-screening method. It would have been also obvious to one of ordinary skill in the art at the time the invention was made to apply a solution containing M13 bacteriophage displaying protein on the surface to an additional ion exchange or filtration as taught by Sartobind® Membrane Adsorbers brochure by Hirai et al. (see method of using

Sartobind S100 cation exchanger, in the middle of left column) with reasonable expectation of success because additional purification step results in more pure product after purification; and one skilled in the art would be motivated to have additional purification for better quality product of a protein of interest.

All physical characteristics of the Sartobind Membrane Adsorbers are already described above, which meets the limitation of Claims 9-12 and 17-19. Fischer-Fruhholz also disclose the Sartobind® Membrane Adsorbers is used for "Clearance of endotoxin" (see page 23), which meets the limitation of method in claim 14. Thus, the invention taken as a whole is *prima facie* obvious.

In response to this rejection, applicants have cancelled Claims 2-5, 7-8 and 16; amended Claims 1, 9, 13 and 15 and added new Claims 17-19; and traverse the rejection for reasons stated below.

Applicants argue that the instant invention surprisingly allows the highly efficient isolation and/or purification of bacteriophage M13 which is a filamentous bacteriophage with a diameter of about 6 nm and length of about 900 nm. Applicants also argue that no one has thought to isolate and/or purify filamentous bacteriophage with help of membrane-based methods since filamentous bacteriophages were thought to be unable to pass the membrane structure, thus only being able to bind to the membrane surface, (ii) filamentous bacteriophages were thought to be hard to elute from the membrane since they easily get mechanically stuck in the membrane structure; wherein the instant invention allows surprisingly high yield with at least 10^{13} bacteriophage M13 per 50 to

100 cm^2 according to instant specification §024-025. Thus, applicants argue that none of Brochure-A, Fischer-Fruhholz, Hirai and Rudgers in view of Hondel in combination teach or suggest the presently claimed invention. See page 7, Remarks filed on 2/11/2009.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. As previously noted, the surprising results as alleged by applicants by reciting the paragraphs "[0024]" and "[0025]", assuming these paragraphs are referring to the application as published [Note applicants are requested to refer only to page and line number of the specification as filed and not to paragraph numbers of the published application in the future as this is the copy of the specification from which the examiner must work and in which the examiner must locate portions reference by applicants], the examiner does not find any surprising and unexpected results because said paragraphs 0024 only describe preferred embodiment of the instant application. Also, "the surprisingly large amount of purified material per surface unit of the membrane" is not a claim limitation and instant claimed method is not limited to any amount of purified material per surface unit. Also, it is well known in the art that increasing the binding partner (or molecules) in a given chromatographic resin increases amount of purified material per surface unit which depends on how one skilled in the art prepare the adsorbing resin. Applicants argue that the process of bacteriophage "passing through the membrane" and "binding to a surface" are as if different processes. However, the bacteriophage always has to bind to the surface of any adsorbing resin which reside on the membrane. Once the property of resin is

shown to bind to a certain bacteriophage regardless of size, one skilled in the art would have no problem preparing an adsorption membrane so that the bacteriophage to pass through the membrane; or using batch binding and elution is also well known in the art which does not have issue of not being able to pass through.

Applicants also argue that a person of ordinary skill in the art would expect large filamentous bacteriophage such as M13 to bind only on the outer surface of the membrane since the Sartobind® Membrane Adsorbers brochure-A is used only for a small virus particle ranging between 45 and 250 nm with icosaedric viruses whereas the bacteriophage M13 is large filamentous virus particle, see page 7, lines 3-14.

As recited in the previous office action mailed on 11/12/2008 (page 13, lines 3-5), the Sartobind® Membrane Adsorbers is made of "cellulose" (see top of page 1) and have pore size of **"3-5 um"** (see top of page 4) which is Sartobind **IDA** (iminodiacetic acid) metal chelate; wherein the instant Example 3 use the identical Sartobind® Membrane, **IDA** (except the brochure A do not recite the type # 19442) having the same pore size range of **"3 to 5 µm"** (see top of page 15, instant specification) to isolate M13 bacteriophage. There is no reason why membrane having the pore size of range of **3 to 5 µm** would not work for M13 bacteriophage which is much smaller (i.e., .applicants acknowledge that bacteriophage M13 has diameter of about 6 nm and a length of about 900 nm. Thus, the bacteriophage M13's diameter 6nm is much smaller than the other icosaedric virus particles (which is roughly shape of globe) ranging between 45 and 250 nm in diameter. It is true that bacteriophage M13 is a filamentous virus which it is long but reasonably flexible (like a noodle, for example). Thus, it is unreasonable to think

that bacteriophage M13 would physically get stuck and can not be eluted in the Sartobind® Membrane Adsorbers given that relatively large diameter (that is larger than 250 nm) particle had no trouble passing through and given the filamentous bacteriophage M13 is thin and flexible (see picture of bacteriophage M13 in the attachment). It is also well known in the art that one skilled in the art would perform a batch binding and separating step when the adsorbing membrane is determined to be undesirable in the step of column chromatography.

As previously noted on page 12, lines 13-17 (see final office action mailed on 11/12/2008) the Sartobind® Membrane Adsorbers brochure-A teach a method of purification using "Sartobind MultiSep Membrane Adsorbers" which is used in chromatography as shown in the figures on page 5, wherein the membrane type includes "Sartobind IDA (**iminodiacetic acid**) metal chelate", wherein the applications includes "Viral purification" (see middle, under the Application on page 6). Since the iminodiacetic acid is the same metal chelating compound as in claimed method, it would binds to the Cu^{2+} which separate bacteriophage M13 from a solution.

Since the Office does not have the facilities for loading and eluting bacteriophage M13 onto a Sartobind® Membrane Adsorbers in brochure-A, the burden is on the applicant to show a novel or unobvious difference between the claimed membrane with iminodiacetic acid charged with Cu^{2+} and the Sartobind® Membrane Adsorbers of the prior art used in a separating bacteriophage M13. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants also argue that while Brochure-A suggests that Sartobind® Membrane can be used for virus purification, it does not suggests the use of Sartobind® metal chelate membranes for the isolation and purification of bacteriophage M13; thus one skilled in the art would not be motivated to purify bacteriophage M13 based in Brochure-A's teachings and Fischer-Fruhholz, Sartobind® Membrane Adsorbers brochure by Hirai et al. and Rudgers et al. and Hondel et al. do not remedy the deficiencies in Brochure-A's teachings.

However, in view of Brochure-A teaching that it can be used in variety of virus and lack of evidence that it can not be used for bacteriophage M13; and given that "M13 bacteriophage represents **the oldest and currently most widely used** protein library-screening method" (see bottom of left column, page 9193 as evidenced by Harvey et al., PNAS, June 22, 2004 Vol. 101, pages 9193-9198, for example), one skilled in the art would be motivated to isolate bacteriophage M13 using the method taught by Sartobind® Membrane Adsorbers brochure-A (available in Sartorius company which is instant assignee) in view of Fischer-Fruhholz (also from Sartorius company), Sartobind® Membrane Adsorbers brochure by Hirai et al. (also from Sartorius company) and Rudgers et al. As noted previously (see bottom of page 11 to top of page 12, final office action mailed on 11/12/2008), "Because one skilled in the art recognize that a virus having a coat protein would bind to a ion chelating membrane and be isolated or removed by the membrane, as long as the coat protein of the virus is capable of binding to metal chelating membrane. The binding of virus to an affinity membrane depends on the coat protein regardless of the virus is filamentous or not; thus, one skilled in the art

knows that Sartobind® Membrane Absorbers having metal chelating binding group can be used to purify any virus including but not limited to any filamentous virus. Furthermore, Fischer-Fruhholz teach that the metal chelate affinity membrane have "affinity to His, Cys, Trp present in almost every protein" (see page 5 of Fischer-Fruhholz) wherein said every protein can be a part of coat protein in any filamentous bacteriophages". Thus, one skilled in the art would be motivated to perform a method of loading bacteriophage M13 and purifying said M13 virus on to Sartobind® Membrane Adsorbers in the brochure-A with a reasonable expectation of success; wherein the motivation for one skilled in the art to purify M13 bacteriophage is provided by Harvey et al. who teach a filamentous bacteriophage M13 is "the oldest and currently most widely used protein library-screening method" (see bottom of left column page 9193).

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Rebecca E. Prouty/
Primary Examiner,
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